

Abstract 886 – Table

	Bladder neck resection margin	Apical resection margin	Peripheral resection margin	Capsular penetration	Seminal vesicles involvement
Concordance rate for positive margin	76%	95%	94%	85%	81%
Concordance rate for negative margin	83%	74%	66%	59%	96%
Conversion rate from negative to positive margin	7%	18%	34%	34%	2%
Conversion rate from positive to negative margin	24%	3%	4%	15%	16%
% of missing information in CH reports	27%	22%	12%	33%	1%
	(10% of these had positive margin on review)	(20% of these had positive margin on review)	(50% of these had positive margin on review)	(38% of these had capsular penetration on review)	

Conclusions: In the TTH review, there was a trend toward GS upgrading. There was a significant discordance rate in the evaluation of resection margins and capsular penetration. Also a significant proportion of CH reports had missing information with regards to resection margin status and tumor extent. The study suggests the importance of central review of RP specimens by a TTH and the need of a standardized reporting system for RP specimens.

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POSTER

Impact of mean rectal dose on late rectal bleeding following conformal radiotherapy for prostate cancer: dose volume effect

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Purpose/Objective: To identify clinical and dosimetric factors predictive of a higher risk of grade 2 late rectal bleeding in patients with localised prostate cancer treated with three-dimensional conformal radiotherapy (3D-CRT) in a prospective dose escalation study.

Methods and Materials: We performed a retrospective analysis of clinical records and dose-volume histograms of 107 patients with T1c-T3 prostate cancer treated at this institution with 3D-CRT and a minimum follow-up of one year. Twenty-one patients were treated at dose level I (70 Gy), 57 patients were treated at dose level II (72 Gy) and 29 patients at level III (75.6 Gy). The mean ICRU reference dose was of 76.49 Gy, range 69.80 to 82.62 Gy. All dose prescriptions were to ICRU point (dose level I) or to the minimum isodose surface encompassing the planning target volume (PTV) (dose levels II and III). Neoadjuvant and 2-years adjuvant androgen suppression were given to 16 and 27 high-risk patients respectively. Late rectal bleeding were graded according to RTOG toxicity scores adapted for rectal bleeding.

Results: Six of the 107 patients (6%) experienced grade 2 rectal bleeding and only one patient (1%) at dose level II had grade 3 complication. The clinical variables considered for analysis were: age, pretreatment PSA, Gleason score, T stage, history of diabetes mellitus and gastrointestinal (GI) diseases, administration and type of hormonal therapy and presence of acute rectal symptoms during radiation therapy. The dosimetric variables considered were: mean ICRU dose, rectal volume, the maximal dose and mean dose to the rectal volume (Dmax and Dmean), NTCP and the volumes (percentage and absolute) of rectum receiving more than 30Gy, 40Gy, 50Gy, 60Gy, 72Gy, 75Gy, 78 Gy and 80Gy. On univariate analysis, only dosimetric factors were significantly correlated with grade 2 rectal bleeding: 1) rectal volume ($p=.024$), 2) rectal Dmean ($p<.0005$), 3) the percentage of rectal volume exposed to >30 Gy ($p=.005$), >40 Gy ($p=.001$), >50 Gy ($p=.001$), >60 Gy ($p<.00005$) and >72 Gy ($p=.016$), and 5) a higher NTCP ($p=0.001$). The results of multivariate logistic regression analysis indicated that both, the rectal Dmean (Exp(B): 1.268; CI 95%: 1.084-1.482; $p=.003$) or V60 (Exp(B): 1.105; CI 95%: 1.036-1.179; $p=.002$) correlated with grade 2 rectal bleeding.

Conclusion: The present study confirms a clear evidence of dose volume effect and the importance of intermediate doses (60 Gy) on the risk of rectal bleeding at this dose level. The predictive value of mean rectal dose could be explained by its strong correlation with intermediate doses and because its real value is less dependent on setup variability and internal organ motion.

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POSTER

Cranial nerve palsies in metastatic prostate cancer- results of base of skull radiotherapy

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Background: Cranial nerve dysfunction caused by metastasis to the base of skull is a relatively infrequent but debilitating complication of prostate cancer that is traditionally treated by external beam radiotherapy and high dose steroids. There is very little data on response to therapy in the literature.

Methods: We examined the Royal Marsden Hospital prostate cancer database for patients with prostate cancer who were treated with external beam radiotherapy to the base of skull for cranial nerve palsies between 1st January 1995 and 31st December 2002. Data obtained included radiological findings, radiation dose and fractionation, biomarkers, and response to treatment.

Results: A total of 32 patients with a median age of 73 years (range 49-85) were identified as fulfilling the inclusion criteria. Increased uptake of isotope was seen in the base of skull in all patients on bone scan. The most common palsies were of the 6th, and 12th cranial nerves. Palsies were unilateral in all cases and multiple in 3 patients (9%). All patients were treated to the mid-plane using parallel-opposed beams of 6 Mev photons or Cobalt-60. Twenty seven patients (84%) received 20 Gy in 5 fractions in 7 days, with 3 patients (9%), treated with 30Gy in 10 fractions. All patients bar one were treated with a median Dexamethazone dose of 6mg daily in addition to radiotherapy. Sixteen patients (50%, 95% CI: 34-66%) had a response to therapy, 50% of which had complete resolution of symptoms. The median survival following base of skull radiotherapy was 3 months (range 1-36) with 14 patients (44%) living less than 2 months after completion of therapy.

Conclusions External beam radiotherapy is an effective modality in the palliation of cranial nerve palsies secondary to base of skull involvement by metastatic prostate cancer with a response rate of 50% in this series. Patients with this manifestation of prostate cancer have a very poor prognosis.

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POSTER

Estrogens and a phytoestrogen (genistein) induce hypersensitivity of prostate carcinoma cell lines to low dose radiation in vitro

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As prostate carcinomas tend to express estrogen receptors (especially type β), we tested the potential of a combined therapy with an estrogen (estradiol) and a predominantly estrogen receptor β -stimulating phytoestrogen (genistein, a soy product) and radiation in LNCaP and PC-3 cells *in vitro*. The advantage of genistein compared to estradiol is its better tolerance in male patients.

With colony forming assays, we tested the clonogenic survival of the cells after incubation with different concentrations of genistein and estradiol and subsequent irradiation.

To evaluate the receptor expression of the employed passages of LNCaP cells, we isolated RNA, transcribed it into cDNA, and performed a hot start RT-PCR.

The influence of the combined treatment on cell cycle distribution was measured by FACS analysis after staining the cells with DAPI.

The LNCaP cells showed no expression of estrogen receptor α , but they did express estrogen receptor β .

Interestingly, we found a marked hypersensitivity to low doses of radiation (0.5–1 Gy) after incubating the LNCaP and PC-3 cells with different doses of the above mentioned hormones. In contrast, the control (irradiation only) followed a linear-quadratic survival curve.

The cell cycle distribution of the cells did not seem to have a major impact on clonogenic cell survival. While incubation with estrogens and phytoestrogens decreased the portion of cells in G1, low radiation doses (0.5 Gy) increased G1 arrest regardless of prior hormone-incubation. This effect could not be demonstrated with high radiation doses (4 Gy).

These *in vitro* results suggest that estrogens and phytoestrogens may induce a hypersensitivity to low radiation doses in these tumour cells. Further investigations focus on the underlying mechanisms, and experiments are currently being repeated *in vivo* using a xenograft model. If these results could also be achieved *in vivo*, this may have important clinical implications.

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POSTER

Acute small bowel and colon toxicity after pelvic IMRT for prostate cancer

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Background: The theoretical advantage of intensity modulated radiotherapy (IMRT) in treating the pelvic nodes (PN) while sparing small bowel and colon has been reported by others (Nutting et al, IJROBP 2000). Here we report acute toxicity rates in 24 consecutive patients treated to date.

Methods: Beginning April 2002, patients with prostate cancer referred to us for definitive radiotherapy and with $\geq 15\%$ risk of PN involvement, were treated as follows: 76 Gy/38 fractions prescribed to the prostate and 54 Gy/30 fxs to the seminal vesicles (SV) and PN. An initial boost to the prostate, delivering 16 Gy/8 fxs was given upfront using a 6-field conformal technique. This was followed by an 8-field coplanar inverse planning IMRT technique delivering an additional 60 Gy at 2 Gy to the prostate and 54 Gy at 1.8 Gy per fraction to the SV and PN. The PN region was delineated on each CT slice taking as landmark the position of major pelvic vessels up to L5-S1. Constraints were set up on the composite dose to the rectum and bladder (V50 and V70) while at least 95% of each target volume (prostate, SV, PN) received the prescription dose. Detailed information on dose distribution to the intestinal cavity (IC) was not available at the time of toxicity scoring. Patients were examined weekly during treatment, and acute toxicity was prospectively scored according to CTC 2.0. The correlation between acute GI toxicity and the absolute amount of IC receiving more than 15, 30, 45, 54, 60 Gy (ABS15&) was investigated. For a given parameter we considered both the maximum toxicity (MT) and the cumulative treatment toxicity (CTT) as the sum of each weekly score. Besides MT (grade 2-3 vs 0-1) and loperamide intake (yes vs no), covariates were categorized by median values and cross-tables were compared with chi-square test.

Results: All patients completed the prescribed treatment. Only one patient had a treatment break (1 week). Small bowel and colon acute toxicity was mild with 4 (17%) patients developing grade 2 diarrhea and 6 patients (25%) requiring loperamide for symptom control. Regarding acute rectal toxicity, 7 pts (29%), 3 pts (12%) and 2 pts (8%) developed grade 2 proctitis, grade 2 rectal bleeding and grade 3 proctalgia, respectively. At all dose intervals but 54 Gy, we recorded a significant correlation between the absolute amount of IC and CTT diarrhea. A trend was found for loperamide. No correlation was found with MT diarrhea and with any rectal toxicity domain.

Conclusions: Treatment of pelvic nodes to 54 Gy at 1.8 Gy per fraction with IMRT as part of definitive treatment to the prostate is clinically feasible with mild small bowel and colon toxicity. For most of dose intervals selected, preliminary data show the presence of a volume/response correlation between the absolute amount of IC and the duration of diarrhea during treatment that, if confirmed, will help to define dose-objectives for IC

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POSTER

Impact of urethrography in high-precision prostate cancer radiotherapy

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Background: Urethrography is commonly used to localize the prostate apex in radiotherapy planning. Data from imaging studies suggest a negligible

systematic error with urethrography, yet fiducial marker studies demonstrate a systematic displacement resulting in inadequate coverage in over 50% of cases. As doses are escalated and margins minimized, previously acceptable motion may no longer be appropriate. We aim to determine if there is a significant systematic error due to urethrography.

Methods: Ten patients with low and intermediate risk prostate cancer, treated with simplified intensity modulated arc therapy (SIMAT), were assessed. Gold seeds were placed at the apex, mid gland and base. Anaesthetic jelly and contrast agent were used during CT-simulation. Setup and organ motion were assessed using fiducial markers via weekly port films and computed tomography. A three-dimensional vector was calculated to assess for centre-of-mass displacement. Margins necessary with and without urethrography motions were calculated based on tumor control probabilities (TCP) and confidence intervals.

Results: The average systematic displacement and standard deviation (in parenthesis) of the prostate from the simulation/urethrography seed location was 0.02cm (0.24), 0.00cm (0.39), and -0.32cm (0.38) in the x, y and z directions, respectively. Urethrography resulted in a three-dimensional cephalad displacement of 0.32cm. A margin less than 6.2mm will result in a 5% reduction in TCP. With urethrography, a 95% confidence interval requires a margin of 1.0cm. Without urethrography, the margin required is 0.6cm. To yield at least a 98% equivalent uniform dose (EUD) for 90% of patients, the planning target volume with urethrography must be 0.87cm.

Conclusion: Using implanted markers and weekly CT scans, we detected a consistent shift of the prostate apex and centre-of-mass cephalad with urethrography. As margins are decreased, alternative methods of localizing the prostate apex should be employed to avoid the possibility of introducing systematic error.

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POSTER

Partial volume irradiation in 3D conformal radiotherapy for the treatment of prostate adenocarcinoma: a poor man's solution to rectum sparing.

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Background: To evaluate the benefit of a new 3D-CRT technique for the treatment of prostate cancer, with special emphasis on the reduction of the volume of rectum irradiated.

Material and methods: a dosimetric study was carried out in 31 patients with organ confined prostate adenocarcinoma (13) or with postoperative PSA failure (18). PTV was an isotropic expansion of 1 cm from the CTV (prostate \pm seminal vesicles). Rectum volume extended 1 cm above and below the PTV. The new 5-field 3D-CRT technique was compared to a standard 4-field CRT.

Study 1, five coplanar, non-coaxial, beams at angles of 0°, 100°, 260° (25 MV), 130° and 230° (6 MV) were used. The two latter beams covered the PTV only partially, with exclusion of the rectum. The weighting of the 5 beams at the isocenter was approximately 100, 100, 100, 15 and 15, respectively. The 100 and 260 beams had a wedge contribution of about 15%.

Study 2: four coplanar beams with gantry angles of 0°, 90°, 180° and 270° were conformed by MLC to the same PTV with a dose weighting to the isocenter of 100, 80, 100 and 80 respectively. 25 MV photon beams were used.

In both studies the plans were optimised to ensure adequate coverage of the PTV by the 95% isodose.

Results. Standard deviation of dose distribution in the PTV was 1.5 and 1.7 for the 4 and the 5 beams technique, respectively. Thus, the 5 beams technique excluding part of the PTV did not degrade the quality of its coverage. The volume of rectum irradiated was reduced at all dose levels. The gain was maximal around the 50% isodose (25% absolute volume reduction), but it was still significant at the 100% isodose (8.5% reduction). The benefit was significant at each isodose level above the 30% isodose (0.01 < p < 0.001). There was no patient in which a benefit could not be demonstrated.

Conclusion: the five 5 beam 3D-technique with partial PTV coverage spares significantly more rectal volume than the standard conformal plan. Insofar as rectum DVH is predictive of rectal tolerance, this technique is expected to significantly reduce rectum morbidity and to allow for dose escalation without resorting to more time-consuming irradiation techniques.